AdverseEvents
REDEFINING DRUG SAFETY

June 17, 2015

Centers for Medicare and Medicaid Services
Department of Health and Human Services
Attention: CMS–2390–P
Mail Stop C4–26–05
7500 Security Boulevard
Baltimore, MD 21244–1850

RE: Medicaid and Children's Health Insurance Program (CHIP) Programs; Medicaid Managed Care, CHIP Delivered in Managed Care, Medicaid and CHIP Comprehensive Quality Strategies, and Revisions Related to Third Party Liability
CMS–2390–P (RIN 0938–AS25)

Dear Sirs:

Thank you for the opportunity to provide these comments on your proposed rule on Medicaid and CHIP managed care (CMS–2390–P). We commend CMS for the hard work and careful thinking that went into the drafting.

Our comments focus on the importance for Medicaid managed care organizations (MCOs) to actively use federal data on post-approval adverse drug events to significantly improve the value of the $28.3 billion Medicaid prescription drug benefit. These drug safety data are available through the FDA Adverse Event Reporting System (FAERS). With more than 1.5 million post-approval adverse drug reactions reported annually to FAERS these data offer invaluable information regarding the real world safety of FDA approved drugs.

Coupled with advanced analytics, rigorous algorithms, and data from the Agency for Healthcare Research and Quality (AHRQ) on the direct medical costs (e.g., hospitalizations) from adverse drug events, managers of drug benefits – whether in Medicaid health plans or in state Medicaid agencies – now have access to far more robust, timely, and evidence-based data regarding the true safety impact and downstream costs of FDA approved drugs. The opportunity to save lives, improve outcomes, and reduce unnecessary costs is considerable, and is now well within reach.

Unfortunately, few health plans and no state currently uses this information when creating preferred drug lists, writing prior authorization criteria, negotiating supplemental rebates, educating prescribers and dispensers, or performing prospective, concurrent, or retrospective drug utilization review. **Absent use of this information, states and health plans spend more money on poorer outcomes, placing beneficiaries at unnecessary risk from suboptimal, costly care and even death and severe disability.** (It is important to note that this information and associated analytical tools are also not used

by Medicare Administrative Contractors when making Part B local coverage determinations or by most Medicare Advantage and Part D drug plans when making formulary and benefit design designs.)

Active use by Medicaid managed care programs of federal data on post-approval adverse drug events for covered drugs and biologics will:

1. Improve outcomes for Medicaid patients by helping ensure beneficiaries receive the safest medication therapy and that both prescribers and dispensers are empowered with the latest information;

2. Identify Medicaid-covered low-risk medications that can be substituted for high-risk drugs in order to reduce beneficiary death and disability;

3. Reduce federal and state costs by preventing hospital admissions, readmissions, and emergency department visits;

4. Improve management of the Medicaid drug benefit, including medical management and drug utilization review functions;

5. Ensure preferred drug lists are developed and updated using all available information, including real-world data on safety and the medical costs of post-approval adverse events, rather than merely emphasizing net unit costs; and

6. Support CMS expectations for comprehensive, evidence-based quality monitoring, improvement, and reporting.

Below, we describe our recommended changes to strengthen the Medicaid drug benefit within managed care programs. Following these recommendations, we provide detailed background information on the use of FAERS data and analytical tools to improve outcomes and reduce costs. To underscore the vital importance of using this information in Medicaid drug benefit management, we include data on adverse events and costs for some therapeutic classes of special importance in Medicaid.

42 CFR Part 431 – State Organization and Administration

42 CFR 431.502 – State Comprehensive Quality Strategy

In §431.502 CMS should clarify that the elements of state comprehensive quality strategy should include identification and reduction of preventable events affecting outcomes and costs, including adverse drug events.

42 CFR Part 433 – Managed Care

42 CFR 438.6 – Special Contract Provisions Related to Payment

In §438.6 regarding payment related provisions in MCO contracts, CMS should encourage states to adopt value-based payment at the plan level which includes reduction of adverse drug events as one of the goals.

42 CFR 438.66 – State Monitoring Requirements

Regarding CMS requirements for state monitoring of Medicaid health plans under §438.66, CMS should explicitly include comprehensive, evidence-based analysis and reduction of adverse drug events, including the use of FDA public data and appropriate analytics, as an additional performance area under §438.66(b).

Regarding state readiness reviews, CMS should expand the list of areas §438.66(d)(4) to include capabilities to assess covered drugs and biologics based on adverse drug events, including the use of FDA public data and appropriate analytics.

42 CFR 438.210 – Coverage and Authorization of Services

Regarding §438.210 on coverage and authorization of covered services by Medicaid health plans, CMS should revise §438.210(a)(4) to require MCOs and other plans responsible for the coverage of drugs and biologics to properly consider post-approval adverse event data when establishing medical necessity criteria, setting prior authorization policies, and placing limits for any drug or biologic.

42 CFR 438.236 – Practice Guidelines

Regarding the adoption, dissemination, and application of practice guidelines, under §438.236(b) CMS should require that Medicaid health plans (MCOs and, when applicable, PIHPs and PAHPs) consider post-approval adverse event data, including FDA public data and appropriate analytics, in adopting practice guidelines related to medication therapy (drugs and biologics, whether physician-administered or self-administered).

42 CFR 438.330 – Quality Assessment and Performance Improvement Program

Performance expectations CMS specifies in the future under the authority of §438.330(a)(2) should explicitly include measures of Medicaid health plan efforts to reduce adverse drug events.

Under §438.330(b) CMS should expand the list of basic elements required for quality assessment and performance improvement programs to include mechanisms to assess and reduce adverse drug events, inclusive of the use of FDA public data and appropriate analytics.

Regarding long-term services and supports (LTSS) performance measurement under §438.330(c)(4), CMS should require measures designed to improve medication-influenced outcomes and reduce adverse drug events in both community and institutional settings in coordination with the appropriate drug benefit payors (whether Part D plan, non-LTSS MCO, or Medicaid fee-for-service).

Under §438.330(d) CMS should encourage performance improvement projects designed to reduce adverse drug events, particularly in high-risk populations and high-risk therapeutic classes.

42 CFR 438.340 – Managed Care Elements of the State Comprehensive Quality Strategy

Consistent with our above recommendation for §431.502, CMS should revise §438.340(b) to require that state comprehensive quality strategies include goals and objectives for the identification and reduction of preventable events affecting outcomes and costs, including adverse drug events.

Background of Adverse Drug Events and Importance for Medicaid

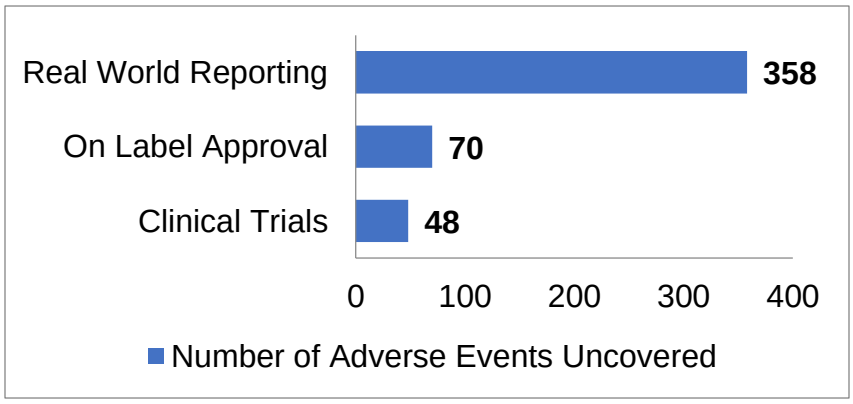
Failing to review and react to the best possible data regarding post-approval adverse drug events puts patients at undue risk and causes significant avoidable medical costs. In 2013, the cost from reported post-approval adverse drug events was approximately $4.7 billion. Some experts believe that up to 90 percent of adverse drug events may go *unreported*, meaning the true cost to the healthcare system may be as much as $25 billion per year.

This has a significant negative impact on patients and clinical outcomes. In 2013, more than 800,000 serious adverse drug events were reported to FDA, resulting in more than **148,000 reported hospital admissions**, **more than 65,000 reported deaths**, and **more than 14,000 reported disabilities**. The FDA expects reports of adverse drug events will soon exceed 2 million annually. An in-depth review of all available post-approval drug safety data can make providers aware of new, serious risks of any medications provided to patients as soon as information on that new risk becomes available.

Practices for formulary decisions are outdated and not using comprehensive data.

Currently, most drug benefit decisions – including preferred drug lists (PDLs) and prior authorization policies in Medicaid – are made using limited information, by considering only the safety and efficacy profiles of drugs based predominately on clinical trial data generated prior to FDA approval of a drug. If a drug shows comparable or superior efficacy versus another, and costs less on a unit basis, it is highly likely to be preferred in benefit designs and PDLs or formularies, and therefore, far more likely to prescribed to patients than alternative drugs. Unfortunately, these analyses ignore the real-world reporting of adverse drug reactions (ADRs) (e.g., injury, hospital admission/readmission, disability and/or death) once a drug is in use among broad patient populations. On average, these real-world reports, which are essential in discovering new drug risks that had not been identified in pre-market drug testing, uncover three-times more ADRs than clinical trials.

Table 1: Post-Approval Adverse Drug Events



Sources: Data from ClinicalTrials.gov; data from FDA Adverse Event Reporting System (FAERS) via AdverseEvents Explorer; Duke, J., Friedlin, J., Ryan, P. (2011) A quantitative analysis of adverse events and "overwarning" in drug labeling. Arch Intern Med. 171(10):944-6.

If managed care formulary decision-makers continue to choose drugs without a thorough analysis of the most current post-approval drug side effect data, they may miss warning signs from emerging data regarding drug side effects, **thereby risking patient safety and increasing healthcare costs**. This is because:

- clinical trials are short-term in nature and include a relatively low number of patients from a restricted population; and
- many serious adverse events only become known after a drug is approved and has been used in varied patient populations.

The good news is that FDA has an existing system – the FDA Adverse Event Reporting System, or FAERS – to gather post-approval drug side effect data. FAERS is the world's most reliable system for discovering new drug risks that had not been identified in pre-approval drug testing. Analysis derived from FAERS data can – and should – be used by managed care plans when making formulary decisions.

Examples of Cost/Outcomes Analysis

State Medicaid agencies and Medicaid health plans are not currently using post-approval drug side effect data to develop and update preferred drug lists, negotiate supplemental rebates with manufacturers, perform drug utilization review, draft prior authorization criteria, educate prescribers and dispensers, or in initiatives to contain costs, improve population health, reduce disparities, and managed care of complex, high-risk populations. This means decisions are based primarily on the net unit cost of prescription medications.

Absent of these data, state Medicaid agencies and Medicaid health plans are not evaluating the total costs of prescribing a drug by factoring in related outcomes such as hospitalizations, disability, or even death. This means that current decisions are not based on all available evidence and can easily lead to false conclusions about safety, efficacy and medical costs that are critical in improving overall quality and performance. **This is a lost opportunity to improve outcomes and reduce costs substantially, particularly for the most vulnerable populations in Medicaid – including children with special health needs and persons with severe mental illness.**

Using publicly available drug side effect data throughout all activities related to the Medicaid drug benefit – particularly for preferred drug lists, utilization review, and care management – is a critical part of quality strategy at the federal, state and plan level. By not using available information, CMS and states are missing an extraordinary opportunity to educate insurers, physicians and prescribers on ways to improve outcomes and reduce preventable events, including hospitalizations, readmissions, and emergency room visits.

Following are examples of how available data can be used to improve formulary decision making in two disease states of critical importance to Medicaid: mental illness and hepatitis-C.

Example 1: Antipsychotic drugs to treat schizophrenia and bipolar disorder

Antipsychotics are used to manage schizophrenia and bipolar disorder and are increasingly being used in the management of non-psychotic disorders. Medicaid is one of the largest payers of antipsychotics, with costs of more than $3 billion per year. This represents millions of patients and more than 10

percent of Medicaid's total annual prescription costs. Additionally, there is concern about over-prescribing, abuse, and pediatric use of antipsychotic drugs.

While Medicaid must cover all antipsychotic drugs, most states use Preferred Drug Lists (PDLs) to steer utilization to drugs with lowest unit price after state-negotiated supplemental rebates. Absent post-approval adverse drug event data, states and their contracted health plans are unaware of the total medical costs and associated outcomes when determining preferred drugs and so naturally prefer lowest-price drugs.

While many schizophrenia drugs have negligible adverse events, data show others to have high rates of death, hospitalization, and other serious, costly adverse events:

- Serious adverse outcome rates vary from zero to 4.44 percent.
- Death rates range from zero to 1.69 percent of patients.
- Hospitalizations caused by adverse drug events range from zero to 2.31 percent, although some drugs have 50 to 100+ times higher hospitalization rates.
- Hospitalizations associated with adverse drug events cost more than **$397 million from 2010-2014**.

Table 2: Schizophrenia Drugs

Brand Name	Serious Outcome Rate	Hospitalization Rate	Death Rate	IME Serious Rate	DME Serious Rate
CLOZARIL	4.4391%	2.3138%	1.6930%	8.1203%	1.0275%
RISPERDAL CONSTA	0.6811%	0.4465%	0.1507%	0.8076%	0.1488%
INVEGA	0.4832%	0.3682%	0.0587%	0.4604%	0.0959%
FAZACLO ODT	0.3870%	0.0639%	0.3003%	0.5239%	0.1022%
SAPHRIS	0.3031%	0.1580%	0.0477%	0.2894%	0.0731%
ZYPREXA	0.2298%	0.1503%	0.0432%	0.4084%	0.0781%
HALDOL	0.1664%	0.0969%	0.0290%	0.2233%	0.0579%
SEROQUEL	0.1270%	0.0813%	0.0234%	0.4281%	0.0682%
LATUDA	0.1162%	0.0753%	0.0112%	0.0598%	0.0112%
FANAPT	0.0854%	0.0503%	0.0140%	0.0831%	0.0152%
SEROQUEL XR	0.0699%	0.0452%	0.0093%	0.1166%	0.0192%
RISPERDAL	0.0786%	0.0485%	0.0136%	0.1118%	0.0242%
GEODON	0.0414%	0.0238%	0.0059%	0.0828%	0.0163%
ABILIFY	0.0415%	0.0268%	0.0052%	0.0508%	0.0103%
PROLIXIN	0.0353%	0.0140%	0.0000%	0.0421%	0.0130%
THORAZINE	0.0205%	0.0091%	0.0043%	0.0266%	0.0064%
COMPAZINE	0.0046%	0.0014%	0.0006%	0.0035%	0.0009%

(*Source: AdverseEvents Explorer®*)

In reviewing outcomes and cost data comparing drugs indicated to treat schizophrenia (see Table 2), Clozaril, for example, shows:

- serious outcome rate more than **6 times higher**;
- hospitalization rate **5 times higher**; and
- death rate **11 times higher** than other drugs in the class.

With respect to bipolar disorder, there are approximately 5.7 million adults, and as many as 750,000 teens, diagnosed with the disease in the U.S. As it is with schizophrenia patients, a disproportionate

number of persons with bipolar disorder are Medicaid enrollees, with most of these individuals served through Medicaid managed care.

The 15 bipolar drugs tracked by AdverseEvents vary widely in rates of serious outcomes and hospitalizations.

- Serious adverse outcomes range from 0.02 percent to nearly 0.68 percent of all patients.
- Hospitalizations from serious adverse events from specific bipolar drugs range from zero to a concerning 0.45 percent.
- Death rates range from zero to more than 1 in 664 patients.
- Severe adverse events involving bipolar drugs resulted in more than **12,000 hospitalizations from 2010-2014**.

Table 3: Bipolar Disorder Drugs

Brand Name	Serious Outcome Rate	Hospitalization Rate	Death Rate	IME Serious Rate	DME Serious Rate
RISPERDAL CONSTA	0.6811%	0.4465%	0.1507%	0.8076%	0.1488%
SAPHRIS	0.3031%	0.1580%	0.0477%	0.2894%	0.0731%
ZYPREXA	0.2298%	0.1503%	0.0432%	0.4084%	0.0781%
SEROQUEL	0.1270%	0.0813%	0.0234%	0.4281%	0.0682%
LATUDA	0.1162%	0.0753%	0.0112%	0.0598%	0.0112%
LAMICTAL	0.0785%	0.0462%	0.0076%	0.1315%	0.0322%
SEROQUEL XR	0.0699%	0.0452%	0.0093%	0.1166%	0.0192%
RISPERDAL	0.0786%	0.0485%	0.0136%	0.1118%	0.0242%
GEODON	0.0414%	0.0238%	0.0059%	0.0828%	0.0163%
SYMBYAX	0.0535%	0.0268%	0.0181%	0.0849%	0.0208%
ABILIFY	0.0415%	0.0268%	0.0052%	0.0508%	0.0103%
DEPAKOTE	0.0300%	0.0142%	0.0023%	0.0430%	0.0093%
PROZAC	0.0179%	0.0049%	0.0038%	0.0287%	0.0055%
ESKALITH	0.0218%	0.0136%	0.0018%	0.0296%	0.0079%
THORAZINE	0.0205%	0.0091%	0.0043%	0.0266%	0.0064%

(*Source: AdverseEvents Explorer®*)

In reviewing outcomes and cost data comparing drugs indicated to treat bipolar disorder (see Table 3), Risperdal Consta, as an example, shows:

- serious outcome rate **2 times higher**;
- hospitalization rate **3 times higher**; and
- death rate **3 times higher** than other drugs in the class.

The estimated annual cost of adverse events per patient is **4 times higher** than other drugs indicated to treat bipolar disorder, as determined by the aggregate cost of serious reported adverse events and outcomes based on costing data from AHRQ's Healthcare Cost and Utilization Project (HCUP).

Example 2: Drugs to treat Hepatitis C

States and Medicaid health plans are currently struggling with cost and clinical issues associated with important breakthrough treatments for Hepatitis C. While data continue to come in, particularly for new treatments such as Harvoni and Sovaldi, a thorough examination of the 6 current (new or old) drugs to treat Hepatitis C shows a significant difference in outcomes and serious adverse events.

Table 4: Hepatitis C Drugs

Brand Name	Serious Outcome Rate	Hospitalization Rate	Death Rate	IME Serious Rate	DME Serious Rate
INCIVEK	8.5464%	7.2307%	0.7299%	11.4281%	3.5966%
INTRON A	3.3369%	2.5257%	0.3238%	3.7994%	0.8203%
VICTRELIS	2.7547%	1.9015%	0.3095%	3.6409%	1.0211%
HARVONI	0.2578%	0.1859%	0.0443%	0.4248%	0.0841%
SOVALDI	0.4960%	0.3487%	0.0986%	0.7157%	0.1614%
OLYSIO	0.8991%	0.6427%	0.1509%	1.3196%	0.3774%

In reviewing outcomes and cost data comparing drugs indicated to treat Hepatitis C (see Table 4), Incivek, for example, shows:

- serious outcome rate more than **2 times higher**;
- hospitalization rate nearly **3 times higher**; and
- death rate **2 times higher** than other drugs in the class.

When Incivek is compared to two new treatments, Harvoni and Sovaldi, differences are even more dramatic, with:

- serious outcome rate **17 times higher**;
- hospitalization rate nearly **21 times higher**; and
- death rate **7 times higher**.

As indicated in these examples, evaluation of post-approval adverse drug event data presents significant opportunity to inform prescription drug decisions, reduce overall costs and improve patient outcomes. Without these data, decisions are based on limited information, meaning states and plans may create preferred drug lists and write prior authorization guidelines that steer prescribers and their patients to drugs that are in reality substantially higher cost and more dangerous. If states and plans continue to only look at net unit price, oblivious to the real net medical costs and patient outcomes associated with adverse drug events, they put Medicaid patients at risk by preferring drugs that lead to overall higher medical costs and poorer outcomes.

Conclusion

We are at a critical stage in reshaping healthcare in this country. As innovation brings advancements in treatments for disease, rising costs, particularly for prescription drugs, threaten our ability to provide quality care to all Americans. We must act to protect high-quality healthcare for those who need it most, without adding more financial burden to our state and federal agencies. CMS has already shown the foresight to align managed care Medicaid plans with existing commercial and exchange plans, setting a high bar for quality and performance. In this spirit, the time is right to safeguard the best interest of patients and the health plans that serve them.

We strongly believe that analysis of post-approval adverse drug event data can improve patient outcomes and lower healthcare costs. Understanding the true impact of a drug must go beyond price and efficacy. Data and healthcare technologies are currently available to enable the review and analysis of:

- serious post-approval adverse events emerging from real world reporting that have not previously identified or listed on the drug's label;

- comparative rate of reported serious outcomes (e.g., hospital admissions, deaths, disabilities) among major drug classes and indications; and
- comparative costs associated with these serious adverse events and outcomes.

Thank you for the opportunity to comment on these important proposed rules on Medicaid managed care. If CMS staff have any questions or wish further information, please contact me at brian@adverseevents.com or (707) 387-9230.

Sincerely,

Brian M. Overstreet
President
AdverseEvents, Inc.